

*FDA Science Board Meeting, November 16, 2001*

Emerging Science Issues in  
Pharmaceutical Manufacturing:  
Process Analytical Technologies

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# Outline

- Emerging regulatory science issue
- An FDA perspective on the current state of pharmaceutical manufacturing
- The promise of modern process analytical technologies
- FDA Science Board's input
  - What steps should the FDA take to facilitate introduction of modern technologies in manufacturing?

# Emerging Regulatory Science Issue

- Scientific and technological advances in the area of process analytical chemistry, engineering, and multivariate data analysis offer new opportunities for improving the overall efficiencies of drug development, manufacturing, and associated regulatory processes.
- Although for many years the pharmaceutical community has recognized the need for improvements in these areas, little progress has been made.

# Discussion Topic

- Process Analytical Technology (PAT)
  - A model (and an initial focal point) to facilitate discussion on of emerging regulatory science issues in pharmaceutical manufacturing
  - Case study - On/in/at line vibrational spectroscopy and imaging tools for R&D and continuous quality verification of quality
  - Other technologies and tools not discussed today but will be considered

# Issue: Need for FDA to Facilitate Introduction of PAT

- Industry is hesitant to introduce PAT in US
  - Regulatory uncertainty/risk leads to “Don’t Tell” or “Don’t Use” practice
    - New Technology = New Questions
      - Method suitability, chemometrics and validation
    - Old products + New technology = New Regulatory Concerns
      - Problems not visible under the current system
  - Mindset: Why change?
    - PAT application will add to current regulatory requirements

# Ensuring High Efficiency of the US Pharmaceutical Manufacturing

- Provide high quality drugs to the US public in a timely manner
- Successfully take advantage of the many new drug development opportunities offered by advances in biology and chemistry
- Ensure optimal utilization of public and private resources to meet the growing health care needs of the US public

# A Perspective on Pharmaceutical Manufacturing

- During Drug Development Phase
  - Process R&D efforts initiated only when there is a reasonable certainty that a drug would be approved
    - In some cases use of “drug powder in a bottle” for early clinical trials
  - Stay with established technologies and systems
    - Avoid technical and regulatory risks
    - Adapt the original research process for scale-up

*G. P. Pisano. The Development Factory: Unlocking the Potential of Process Innovation. 1997, Harvard Business School Press, Boston, MA.*

# A Perspective on Pharmaceutical Manufacturing

- After approval
  - To increase capacity, it is often considered less risky to maintain the current system and invest in additional plants and equipment
    - *G. P. Pisano. The Development Factory: Unlocking the Potential of Process Innovation. 1997, Harvard Business School Press, Boston, MA.*
- When is the “right” time for process improvements and innovation?

# When is the “right” time for process improvement?

- For a few products - never?
  - *A 1997 FDA Warning Letter: XXX time release pellets are prepared by hand coating XXX powder. ... This manual process results in formation of agglomerates and in an accumulation of ingredients on the sides of the coating pan. Operators sporadically scrape this undistributed material .... manually break up agglomerates ....and crushing them during processing*

# Regulatory risks/uncertainty for process improvements

- Process changes can require extensive additional testing to ensure unchanged safety and efficacy profile
  - Prior regulatory approval
  - Scale-Up and Post Approval Changes (SUPAC) guidance documents

# Current State: Dosage Forms

- For human drugs the oral route of administration is the preferred and predominant route
  - Evolutionary trend: Dosage forms -to- Drug Delivery Systems -to- Intelligent Drug Delivery Systems

# Current State:Pharmaceutical R&D and Manufacturing

- The principles of pharmaceutical product design originated in the art of pharmacy compounding
- Over the past century these practices have steadily been reinforced with science and engineering principles
- Most dosage forms are complex multi-factorial physico-chemical systems
  - Reliance on empirical approaches for identifying optimal product and process conditions

# Current State: Optimization

- A (high) degree of uncertainty on the impact independent variable(s) have on product quality and performance
  - One-factor-at-a-time experimentation often only provides information applicable to the conditions tested.
  - Uncertainty with respect to “critical” process variables
  - Limited data available at the time of establishing regulatory specifications

# Current State: Material Science

- Many functional (e.g., physical) attributes of pharmaceutical materials not well characterized
  - Official monographs (USP-NF) focus only on chemical identity and purity/impurity
    - It may not be feasible/practical to define “functionality” in official monographs

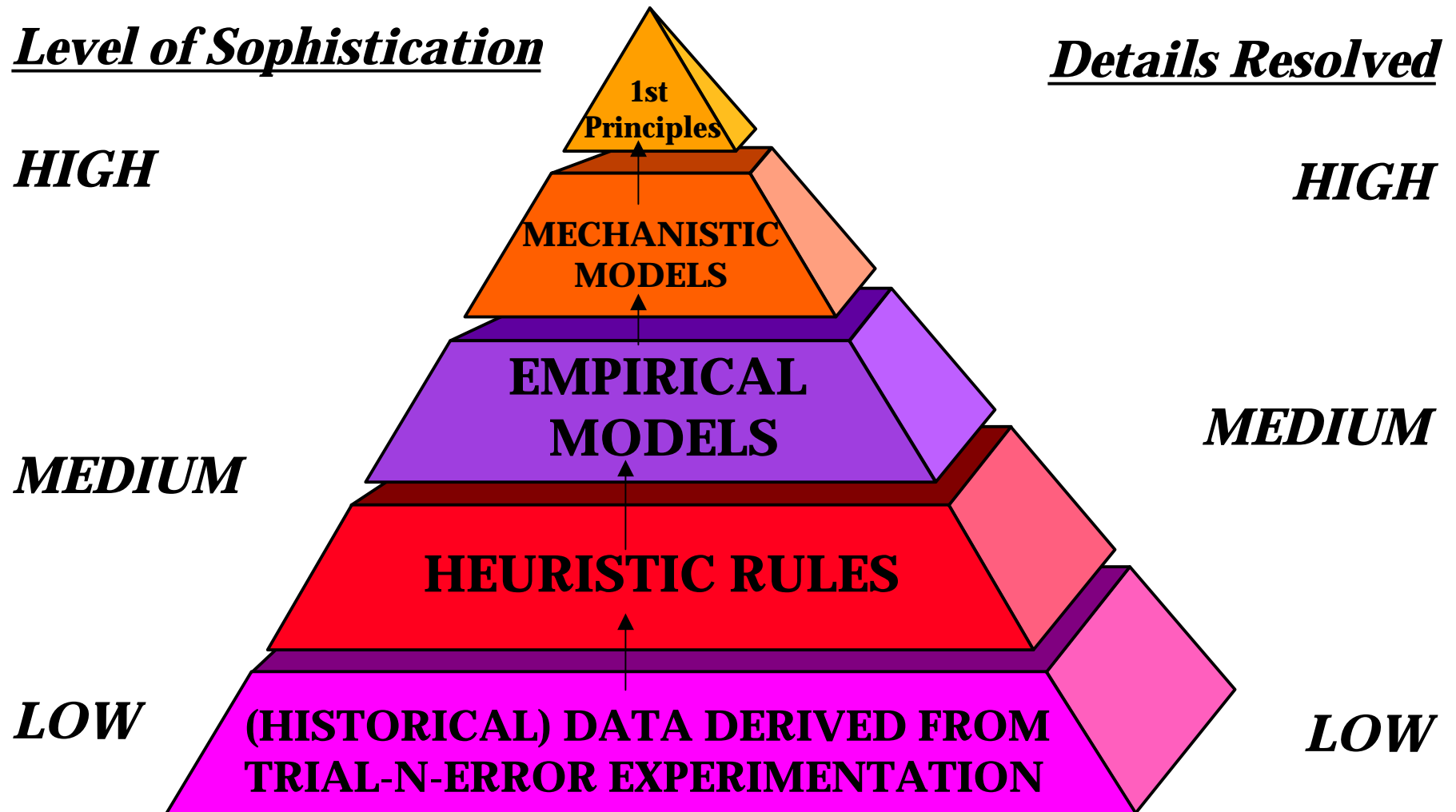
# Regulatory Challenge: Managing Changes

- Absence of causal links or correlation between performance attributes and process variables
  - Extensive additional testing and prior approval
- New challenges - limited product development time and resources
  - Significant formulation and process changes often necessary during scale-up and technology transfer
  - Several "bridging" studies (e.g., human bioavailability and accelerated stability testing) needed to ensure unchanged safety and efficacy profile

# Current Quality Control Paradigm

- *Testing* to document quality
  - Predominantly “wet chemistry” tests
- Quality can not be tested into products, it needs to be “built-in”

# Quality by Design? Product Development Knowledge (Public Databases or in Submissions)



# An Example: Current Regulation of Powder Blending Operations

- A indicator of the current state of regulatory science (?)
- Continuing industry-FDA debate on how to assure “*adequacy of powder mix*”
  - What is this debate all about?
    - Assuring quality or documenting quality
    - Representative samples
    - Art Vs. Science
  - Test Vs. Control

# A question of “representative sample”?

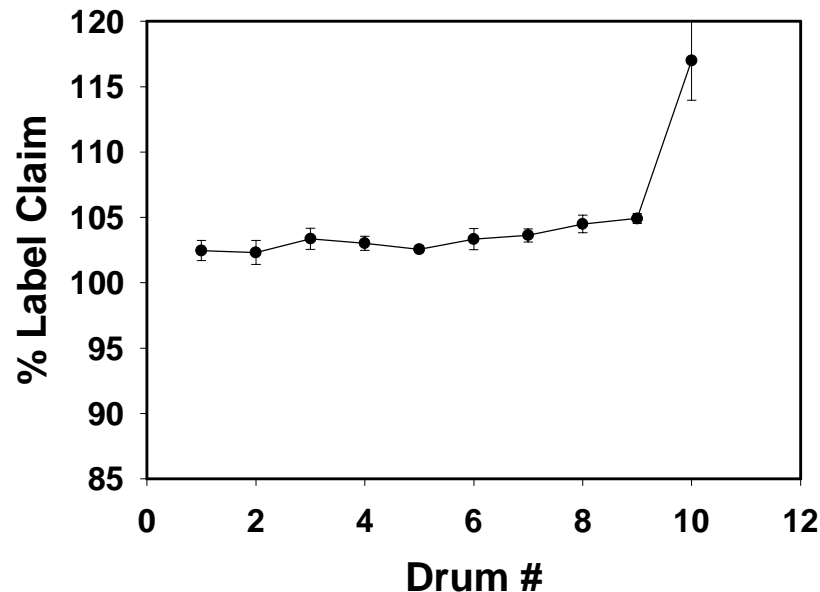
**Blend Sample Analysis  
(Thief)**

**%RSD = <1 PASS**

**USP Content Uniformity  
Stage 1: PASS**

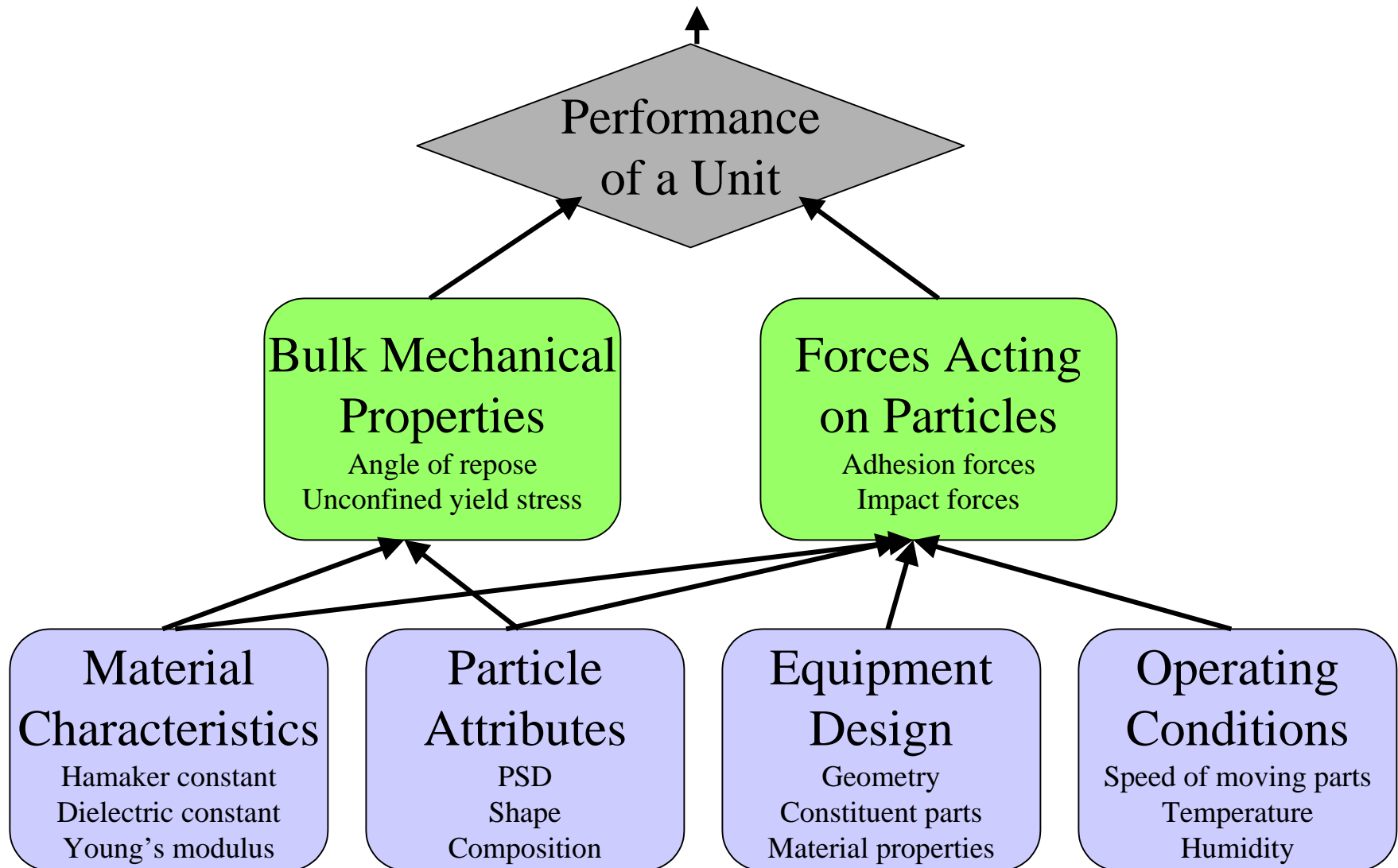
## **PQRI Proposed Stratified Sampling**

**Content Uniformity Data  
on Tablets (Prod. D, Comp. X)**



# Performance of a Solids Processing Units

AIChE Journal 47: 107-125 (2001)



# Today Trial-Error is the Norm

Do SOP's reflect established Heuristic rules?

**Segregation is not a serious problem if all the particles are smaller than 30 um or if they are slightly moist** Establish acceptance criteria for particle size distribution of excipients

Avoid bulk solids transfer where particles slide down a long, inclined chute

Segregation due to percolation is likely to be a concern if the particles of different density or size are poured into a heap or let slide on an inclined chute

The tendency of segregation of binary mixtures due to percolation decreases substantially if the ratio of particle diameters is lower than 1.3

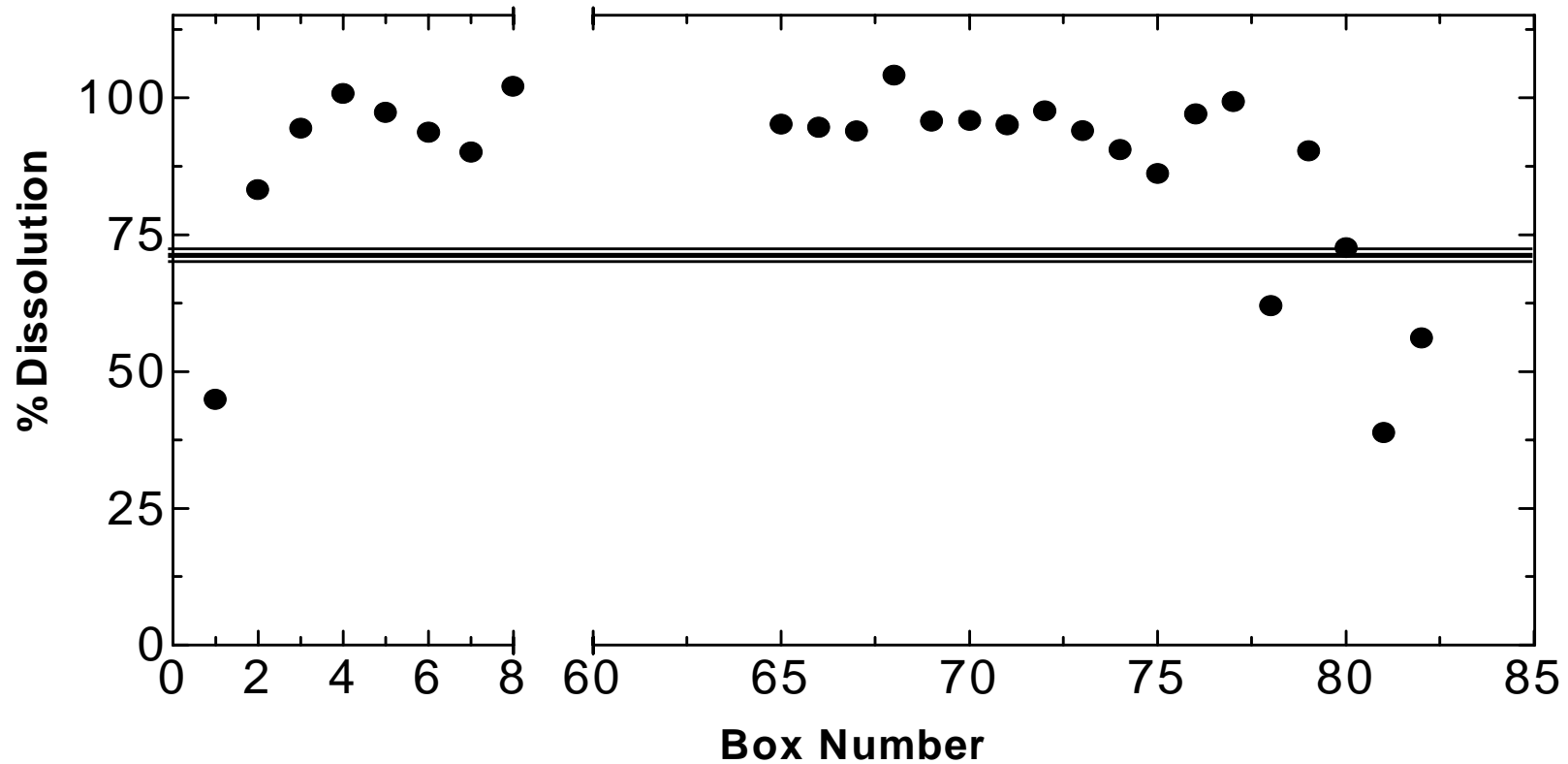
Ensure mass flow in hoppers

Segregation during emptying of a storage unit is accentuated when funnel flow occurs

# Advantages of PAT for Blending

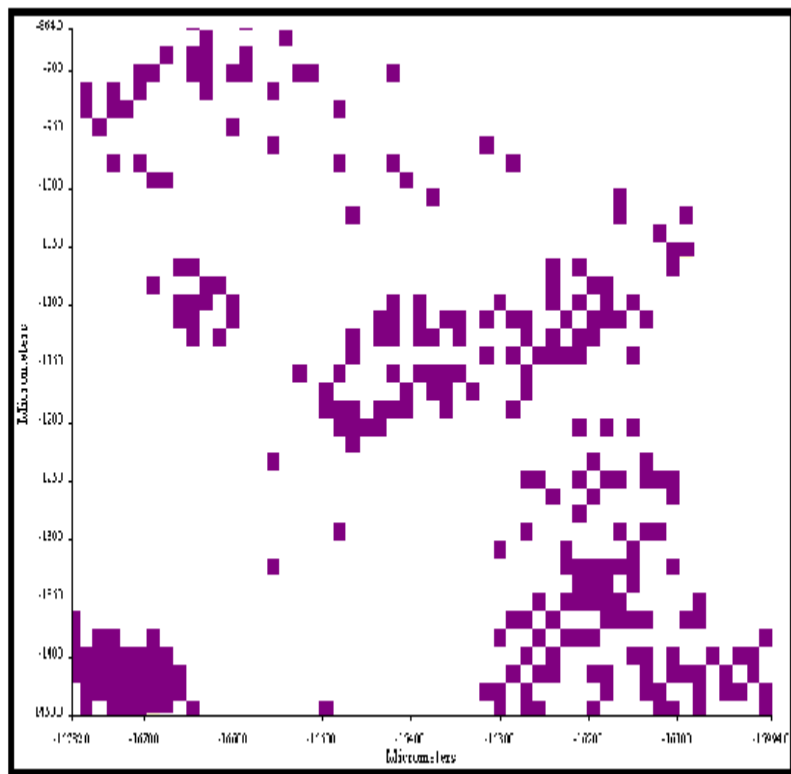
- Paradigm shift towards (feedback) control
  - Cycle time reduction, reduce scrap,...
- Help to “build quality in”
  - Improved and efficient control of raw materials (particle size, packing, moisture)
  - Process data to aid in scale-up, modeling,...
  - Adequacy of mix with respect to all critical components
  - Multiple/critical locations (e.g., blender and/or hopper) in the process to minimize the likelihood of “segregation” post blending step

# Non-homogeneous distribution of Magnesium stearate

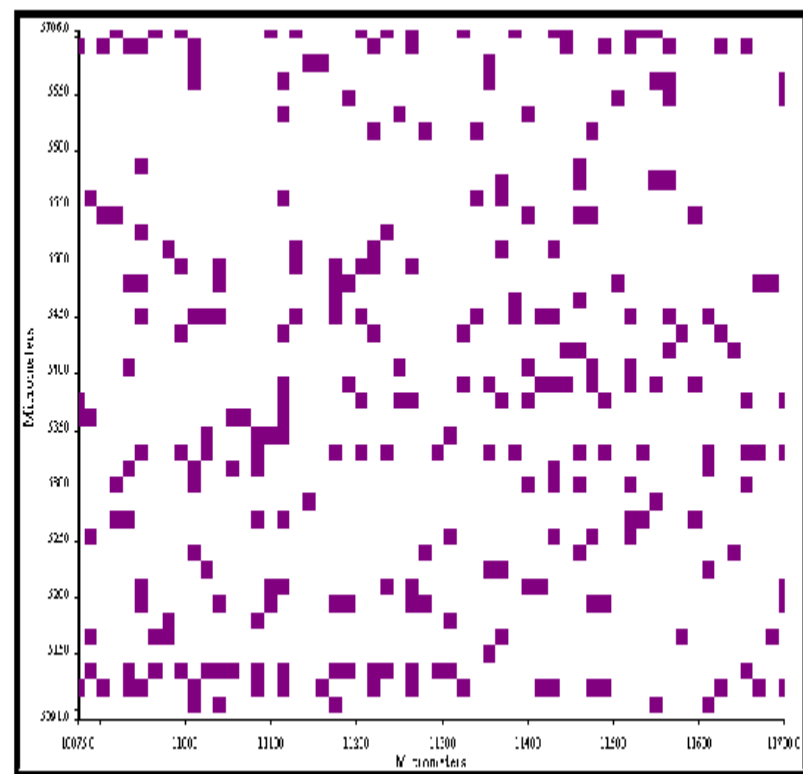


# Is Content Uniformity of “Critical” Excipients Such as *Mg. Stearate* Important?

Distribution of Lubricant in Blend



**Bad Flow Blend**

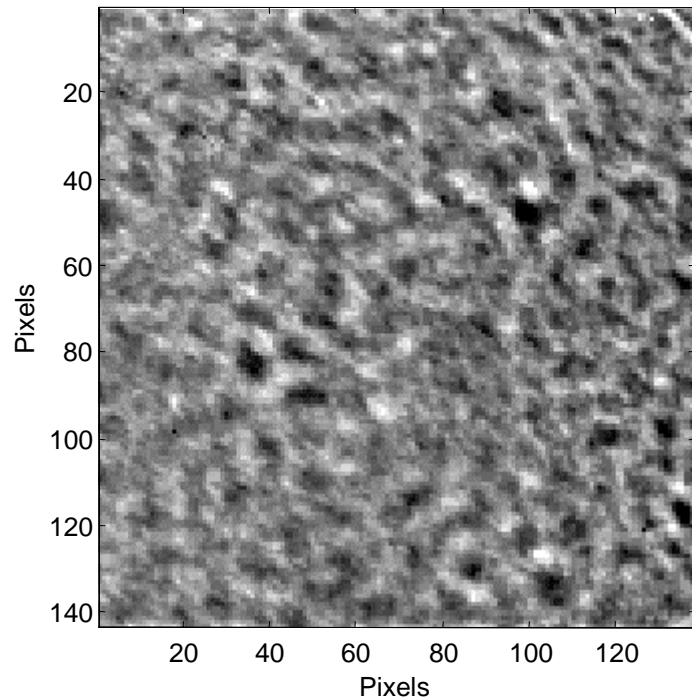


**Good Flow Blend**

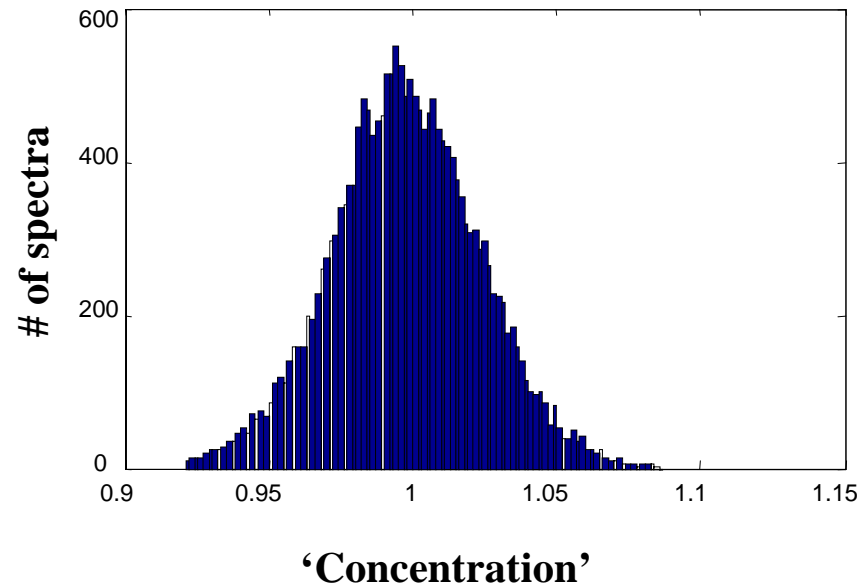
*S. Hammond, Pfizer*

# At-Line Assurance of Content Uniformity

Near-infrared Chemical Image



Sample distribution



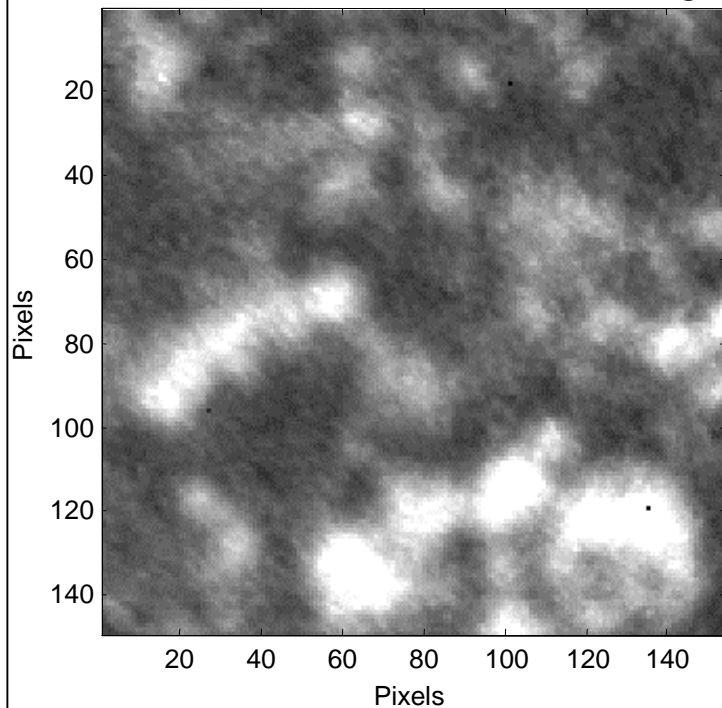
Mean = 1.0

normal symmetric distribution

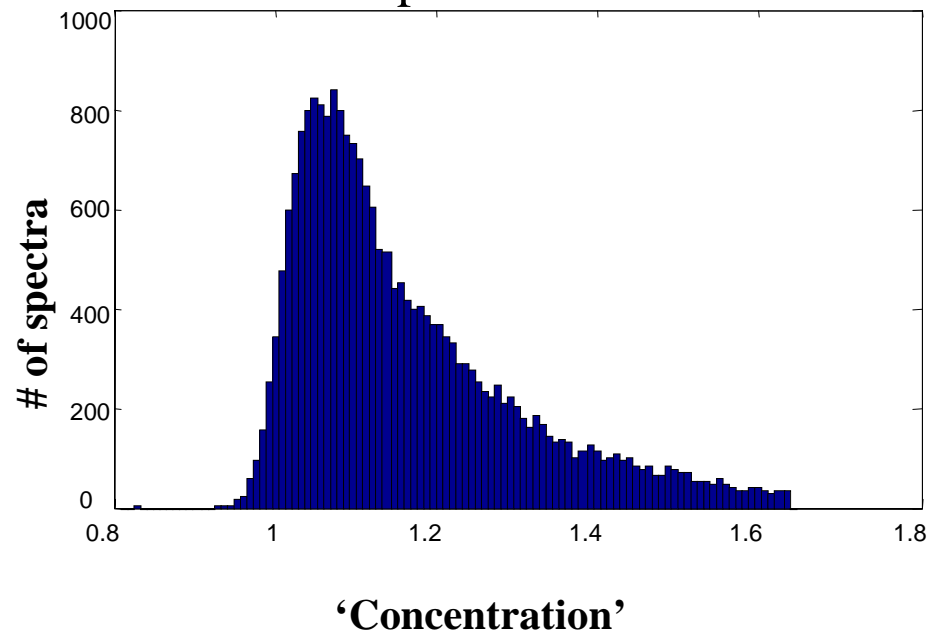
*Lyon, Lester and Hussain. OPS/CDER/FDA 2001*

## At-Line Assurance of Content Uniformity (Poorly Blended Preparation)

Near-infrared Chemical Image



Sample distribution



Mean = 1.2

very asymmetric distribution

# Beyond Blending

- Conventional
  - Compendial tests for excipients
  - Blending
    - BUA Testing (drug only)
  - Compaction
    - Hardness, thickness, weight, friability
    - Content uniformity
    - Dissolution
- NIR/LIF (on-line or at-line)
  - Identification and characterization (moisture, particle size,....)
  - On-line control of adequacy of mix with respect to all components
  - On/at-line assurance of acceptable hardness and (friability)
  - On/at-line assurance or control of content uniformity
  - On/at-line assurance of dissolution rate

# “Win-Win” Opportunities

- Optimal application of modern process analytical technologies can
  - Improve quality and manufacturing efficiency
  - Reduce the likelihood of scrap/recalls
  - Improve the scientific and engineering basis of many current FDA-Industry debates


# Potential to Reduce Scrap and Recalls

- A large % of OOS and recalls due to deviation in physical attributes (e.g., dissolution)
- Prevention: focus on feedback control of process
  - Improve raw material/vendor qualification and screening
  - On/in/at-line control of critical physical and chemical attributes
    - Correlate with quality/performance
  - Support development of more robust processes
    - A higher level of process understanding will be necessary for optimal application of PAT

# Industry-FDA Debates

- Performance based specifications and critical process controls
- Eliminate certain types of SUPAC changes
  - process until optimal attributes are reached
- Reduce the need for process changes
  - improved screening and qualification of raw materials
- May reduce the need for additional testing
  - Improved measures of functional attributes that may correlate with quality/performance



# What Should FDA Do to Facilitate Introduction of PAT?

- Eliminate regulatory uncertainty
  - Official position - FDA will accept new technology that is based on “good” science 
  - Develop standards for PAT
    - Method suitability and validation
    - Multivariate statistical/computer pattern recognition
    - Critical process control points and specifications
    - Changes
    - OOS....

# What Should FDA do to Facilitate Introduction of PAT?

- Define a clear science based regulatory process
  - Current system “adequate for intended use”
  - Introduction of PAT not a requirement
  - Define conditions under which PAT may replace current “regulatory release testing”
  - Process for addressing existing “invisible” problems in marketed products
  - Review and inspection practices
  - International harmonization

# How Should FDA Facilitate PAT?

- Limited institutional knowledge and experience at FDA
- Seek input and collaboration
  - Advisory Committee for Pharmaceutical Science
    - Subcommittee on PAT 
  - Industry (individual companies?)
  - Academic Pharmaceutical Engineering and Process Analytical Chemistry programs
  - PQRI 

# Questions for the Science Board

- Are you able to support the approach?
- What resources do you suggest FDA draw on?
- Are there additional aspects to regulation of product quality that we should focus on?